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AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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OPHTHALMIC DEVICES PANEL

101ST MEETING

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Friday, July 20, 2001

9:35 a.m.

Main Conference Room
9200 Corporate Boulevard
Office of Device Evaluation
Rockville, Maryland

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PROCEEDINGS

Call to Order

DR. SUGAR: I would like to call this meeting of the Ophthalmic Devices Panel to order. We will have introductory remarks from Sara Thornton.

Introductory Remarks

MS. THORNTON: Good morning and welcome to the 101st Meeting of the Ophthalmic Devices Panel. Before we proceed with today's agenda, I have a few short announcements to make. Bear with me. I would like to remind everyone to sign in on the attendance sheets in the registration area just outside the room here. All the handouts for today's meetings are available at the registration table.

Messages for the panel members, the FDA participants, information or special needs should be directed through Ms. Annemarie Williams or Mr. Demarc Thompson who are available in the registration area. If you need the phone number for someone to reach you out there, it is 301 443-8011.

In consideration of the panel, the sponsor and the agency, we ask that those of you with cell

phones and pagers either turn them off or put them on vibration mode while in this room.

We ask that all panel meeting participants speak into the microphone and give your name clearly so that the transcriber will have an accurate recording of your comments.

The next Ophthalmic Devices Panel Meeting will be on Friday September 21, 2001. All available information for that meeting will be on the FDA Advisory Committee website within the next few weeks. Should the September meeting be held here, we will be pleased to be able to invite you back to enjoy new carpeting and thorough painting that have taken place in your absence.

Now, at this time, I would like to extend a special welcome and introduce to the public, the panel and the FDA staff four new panel consultants who are with us today for the first time.

Dr. Timothy Edrington is a Professor of Optometry and Chief of the Cornea and Contact Lens Service at the Southern California College of Optometry in Fullerton, California.

Dr. Timothy McMahon is as Associate Professor of Optometry in the Department of Ophthomology and Visual Sciences at the University

of Illinois at Chicago.

Dr. Barry Weissman is Professor of Ophthalmology and Chief of the Contact Lens Service of the Jules Stein Eye Institute and Department of Ophthalmology at the UCLA School of Medicine.

Dr. Karla Zadnik is an Associate Professor of Optometry and Physiological Optics at Ohio State University College of Optometry and a Glenn A. Frye Endowed Professor since 1999.

We greet you as special government employees and welcome you to the panel table today.

To continue, will the remaining panel members please introduce themselves beginning with --

DR. SUGAR: Ralph, we can start with you.

DR. ROSENTHAL: Ralph Rosenthal. I am the Division Director.

DR. WEISS: Jayne Weiss, panel member.

DR. GRIMMETT: Michael Grimmett, Bascom Palmer Eye Institute, Miami, Florida.

DR. MATOBA: Alice Matoba, Baylor College of Medicine, Houston, Texas.

DR. JURKUS: Jan Jurkus, Illinois College of Optometry in Chicago.

DR. SUGAR: Joel Sugar, University of

Illinois at Chicago.

DR. PULIDO: Jose Pulido, University of Illinois, Chicago.

DR. BANDEEN-ROCHE: Karen Bandeen-Roche, Johns Hopkins University, Baltimore.

DR. YAROSS: Marcia Yaross, Allergan, Irvine, California and industry representative to the panel.

MS. THORNTON: Thank you, panel. I would like to note for the record and with regret that Ms. Lynn Morris, our panel consumer representative cannot be with us today. Earlier this week, she fell and broke her ankle and is doing her best to rest comfortably at home. We wish her well and look forward to having her with us at the next meeting.

I am your executive secretary, Sara Thornton.

Conflict of Interest Statement

MS. THORNTON: I will now read the conflict of interest statement for the record. The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety.

To determine if any conflict existed, the agency reviewed the submitted agenda for this meeting and all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interest.

However, the agency has determined that participation of certain members and consultants, the need for those services outweighs the potential conflict of interest involved, is in the best interest of the government.

Therefore, a waiver has been granted for Dr. Karla Zadnik for her financial interest in a firm at issue that could potentially be affected by the panel's recommendations. The waiver allows this individual to participate fully in today's deliberation. A copy of this waiver may be obtained from the agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

We would like to note for the record that the agency took into consideration other matters regarding Drs. Karen Bandeen-Roche, Timothy Edrington, Timothy McMahon, Barry Weissman and Karla Zadnik. These individuals reported past or

current interest in firms at issue but in matters that are not related to today's agenda.

The agency has determined, therefore, that they may participate fully in all panel deliberations. In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement and the exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

Appointment to Temporary Voting Status

MS. THORNTON: I would like to read now the appointment to temporary voting status. Pursuant to the authority granted under the Medical Devices Advisory Committee charter dated October 27, 1990 and as amended August 18, 1999, I appoint the following individuals as voting members of the Ophthalmic Devices Panel for this meeting on July 20, 2001; Dr. Karen Bandeen-Roche, Dr. Timothy Edrington, Dr. Timothy McMahon, Dr. Barry Weissman,

Dr. Karla Zadnik.

For the record, these individuals are special government employees and consultants to this panel or other panels under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting. Signed Dr. David W. Feigal, Jr., Director, Center for the Devices and Radiological Health, June 28, 2001.

Thank you, Dr. Sugar.

DR. SUGAR: Thank you, Sally.

We will now move to the Open Public Hearing. We have thirty minutes so I presume each of the three presenters will limit themselves to ten minutes and will start out their presentation with a statement of any financial interest and who is sponsoring their appearance here.

Dr. Holden?

Open Public Hearing

DR. HOLDEN: Thank you, Mr. Chairman and thank you for the opportunity of saying a few words. I have documented in the notes that were distributed our commercial linkages. They include royalty arrangements and intellectual property

development with a variety of corporations including Ciba Vision.

The government of Australia makes it mandatory for us, when we develop intellectual property, to receive royalties and those royalties are distributed according to the contract with the government. We, indeed, have collaborative projects which are intellectual property and royalty generating with the organizations listed on the slides.

What brought me to Washington by way of money was money from my own organization. I am not sponsored to speak here nor do I have any shares in any company other than Tulstra, Australia. I have never bought shares in the ophthalmic industry so I don't gain to benefit in that way. My organization certainly does gain to benefit from both consulting and collaborative money.

[Slide.]

The main reason I am here is because this is an extremely historic occasion for the consideration of extended wear and the genius of Otto Wichterle back in the '60's both predicted and worked on daily exposables and extended wear in his time.

[Slide.]

I thought I would show you what thirty years of extended-wear research has done to me, Mr. Chairman.

[Slide.]

The problem we have had is microbial keratitis. It is the only serious adverse event as defined by Stulka and others in the literature as it can lead to significant loss of vision.

[Slide.]

It was another genius, Montague Ruben from Moorfields Eye Hospital, that blew the whistle on extended wear back in the early '70's in particular in soft-lens extended wear for aphakic patients.

[Slide.]

There are a variety of studies that I have listed in my handout. The classic one in 1989 was Poggio, Glynn and Schine and colleagues where ulcerative keratitis in extended wear was at the rate of 21 per 10,000 people or 1 in 500 people, five times greater than with daily wear.

[Slide.]

Many may not know that ten years later, another landmark paper was published by Cheng et al. in Lancet showing 1 in 500 or 20 per 10,000 was

still the norm for extended wear of current hydrogen lenses at that time, although the situation for daily wear seemed to have been improved as there was an 8.3 times less risk with current daily-wear lenses.

[Slide.]

In our studies over the last ten years or so with low-Dk soft extended wear that have involved about 2,278 eye years and about 1,000 wearers, we find a much higher rate of microbial keratitis in those wearers at 2.5 times, Poggio, in fact, in these prospective case-control studies.

[Slide.]

In fact, for every 191 patient years of extended wear of current hydrogels, we find a case of microbial keratitis. In fact, the survival analysis shows us that, over time, the number of people being affected is quite substantial. The last point there is a patient of ours who we have been following for five years, one of 37 patients, in fact, who has just recently had microbial keratitis.

[Slide.]

However, despite the issue of microbial keratitis, the loss of best-corrected visual acuity

has relatively been an underplayed variable in our understanding of these issues. In fact, if you look at Cheng and Nilsson's paper, the loss of two lines of best-corrected visual acuity is at a rate of 1 in 40,000 contact-lens wearers.

With extended wear, it averages about 1 in 12,000 contact-lens wearers.

[Slide.]

This is in comparison, if you like, to LASIK where the loss of two lines best-corrected visual acuity is 1 in 32, some 300 to 1,000 times higher than it is with contact lenses.

[Slide.]

Of course, that is not unexpected as contact lenses have only really one really sight-threatening side effect whereas LASIK, in fact, has a number.

[Slide.]

If we look at the intraoperative complications, the postoperative complications and, indeed --

[Slide.]

-- the summary of the two that is recorded in the handouts that I have prepared, an average of 3.2 percent is the literature figure these days for

significant complications following LASIK leading to a 313 per 10,000 complication rate.

[Slide.]

Not coincidently is the loss of two or more lines of best-corrected visual acuity with LASIK is also recorded in the literature averaging around 3.1 percent or 1 in 32 people.

[Slide.]

Turning back to contact lenses, we knew from 15 to 20 years ago and the research by many people from the United States, Europe and Australia, that the major problems that we have had with infections have been somewhat related to the sickness of the epithelium continuing with current materials on extended wear.

The closed-eye environment is virtually anoxic with current lenses for extended wear leading to a thin, attenuated poorly metabolizing epithelium. The adherence of pathogenic bacteria is increased and if patient is in the circumstance where they introduce massive numbers of bacteria, infection can, indeed, result.

[Slide.]

So the hypothesis starting out some 15 years ago or maybe even earlier than that, 20 years

ago, was that hypoxia would provide a healthy epithelium and better able to resist for the eye infection.

[Slide.]

In 1994, George Mertz and I published what we thought was necessary to avoid hypoxia with contact lenses.

[Slide.]

Since both the Bausch & Lomb and Ciba Vision lenses have been released for experimental and clinical use around the world, in fact, this data from Fonn shows the overnight swelling response with high Dk soft is very low compared with the lenses that are on market at the present time.

[Slide.]

Perhaps more importantly, the ongoing clinical indicators, particularly microcysts, show that, compared with low Dk soft lenses, high Dk soft lenses have virtually no microcyst response.

[Slide.]

A colleague of mine, Eric Papas, has shown that, as you increase oxygen transmissibility to the levels we see today, limbal redness actually disappears.

[Slide.]

In fact, although the lighting is poor here, we would see that vascularization of the peripheral cornea, when patients are refitted with high Dk soft, those vessels unfill, if I can use that term.

[Slide.]

Of course, Dwight Cavanagh and colleagues have documented with human epithelial cells the decrease in adherence of Pseudomonas with the wear of higher oxygen-permeability contact lenses.

[Slide.]

So what is our situation with regard to the risk of microbial keratitis? We have been looking at about 1,000 eye years of patients with microbial keratitis being our number-one requirement for these studies. As yet, we have found no cases of microbial keratitis over these 1,000 eye years.

[Slide.]

When we look at the survival analysis of the two, we are only at the p equals 0.09 stage for significance of difference, but there is obviously a difference in trend. That is promising, but it is not conclusive.

[Slide.]

When we pool the data from B&L and Ciba Vision premarketing and research studies --

[Slide.]

-- we get an eye-wearer figure of around 3,000 eye years.

[Slide.]

When we look at the figure from Cheng et al., 48 microbial keratitises out of 24,000 Dutch contact-lens as opposed to 0 out of 3,000. That also, indeed, looks promising.

[Slide.]

In the marketplace, there has been an influx of contact-lens wear of high Dk extended wear. As yet, there is one report that we have received and we are monitoring these things as closely as we can, in the last week, in fact, of microbial keratitis in the 55,000 wearers in the United Kingdom.

[Slide.]

In Australia, high Dk soft has been on marketplace for 24 months.

[Slide.]

In the first year, it captured 5 percent of contact-lens wearers and it is actually doubling

every 12 months with two-thirds of the patients on 30 nights extended wear and one-third on daily wear.

[Slide.]

Currently, 13 percent of all new patients and 30 percent of refits are wearing high Dk soft lenses, according to the data recently published by Wood and Morgan.

[Slide.]

So, indeed, the penetration rate in Australia of the contact-lens market is around 13 percent.

[Slide.]

There have been four events of microbial keratitis in Melbourne reported recently seen at the Victorian Eye and Ear Hospital. All were 16 to 22-year-old males. Maybe swimming was a factor. Two occurred with each lens type on the market. Three of them were culture positive but none were Pseudomonas. Two of them resolved to 20/25 and two had no effect on vision.

[Slide.]

If we look at that rate, we are talking about 1 in 16,000 wearer years being an indicated figure for microbial keratitis, MK, in Australia.

[Slide.]

Globally, there are about 250,000 wearers of high Dk soft with about 175,000 patient years. There are 9 MK case reports that we received. Four have led to one line loss of acuity, three no effect and two we don't have the data, one in Italy, one in France, one in the U.S., four in Melbourne, one in the U.K. and one in Norway.

At that rate, 9 in 175,000 wearer years looks fairly promising compared with the previous experience.

[Slide.]

If we take the worst case for Victoria, 20,000 high Dk soft-lens wearers in Victoria, four that we know about and, perhaps, four that we don't, we are still looking at a factor of some six times less microbial keratitis per wearer year than in low Dk soft lenses.

[Slide.]

So, globally, that is very promising. What is even more promising is that there are yet to be reported any cases of loss of visual acuity of two lines or more of best-corrected visual acuity in the 175,000 wearer years that have so far existed around the planet.

[Slide.]

So where do we go from here? Microbial keratitis is the only contact-lens serious adverse event that is likely to occur with high Dk soft. High Dk soft looks very promising but we need continued postmarket surveillance targeted at the annualized incidence of microbial keratitis especially recording visual outcome. Such studies need to collect that data.

[Slide.]

In addition, the world needs a gold standard, properly controlled, scientifically valid benchmark study of the prevalence and relative risk of microbial keratitis and with colleagues around the world, we are undertaking such studies.

Thank you very much for your attention

DR. SUGAR: Thank you, Dr. Holden.

Dr. Deborah Sweeney will now give the next presentation.

DR. SWEENEY: Good morning.

[Slide.]

Thank you for this opportunity. I have no commercial interest in any ophthalmic industry and Professor Holden has already outlined the commercial linkages of the CRCERT and CCLRU which I

am employed by and CRCERT and CCLRU have provided the funding for my attendance here today.

What I hope to do briefly is talk to you about what we feel is the value or the worth of the development of these new high-Dk silicone materials and what that means to both our patients and us as practitioners.

[Slide.]

In surveys conducted at the CCLRU of nearly 1500 patients that have either been wearing contact lenses or are interested in contact-lens wear, when questioned about their preferred mode of wear, we can see overwhelmingly that patients are interested in being able to wear their lenses where they can sleep in a modality either in extended wear or a continuous-wear basis.

[Slide.]

Other surveys have recorded what we know as practitioners to be the case that contact-lens wearers are very interested in being able to see in the morning on awakening. 79 percent of the patients in this survey had considered refractive surgery but had not elected to have the procedure and 65 percent report that their contact-lens care and routine interferes with their lifestyle.

[Slide.]

A group of educators earlier this year looked at the area of the patient wanting to feel normal, to be without any correctional vision problem and so rated their impression of the average patient's desire for achieving continuous vision with freedom of spectacles and over 70 percent rated this desire as very high.

[Slide.]

So, as our patients want a variety of factors or needs to be met from their vision correction, the primary two are comfort, particularly with contact lenses -- they want to be unaware of these lenses -- they want a no-fuss and no-bother modality of vision correction.

Together with the LV Prasad Institute in India and the CCLRU, we have conducted a number of prospective clinical studies on both neophytes and experienced in a range of modalities from spectacle wear, daily wear, daily disposable, conventional extended wear and of continuous wear.

[Slide.]

As part of these studies, as well as collecting the clinical data, we also survey our patients of their attitudes and administer

questionnaires regarding their attitudes and satisfaction with both continuous wear, their previous lens experience and their attitudes to LASIK.

[Slide.]

In this group of 80 patients that have experienced continuous wear for an average 12 months, when we ask these patients what they liked most about being able to wear lenses on a 30-night wear schedule, overwhelmingly, the main reason for liking this modality is the convenience that it offers as well as their ability to see in the morning and comfort.

[Slide.]

This issue of convenience and what it offers to our patients, when we look at the different modalities here, is quite obvious. Here, in daily wear, 30 percent, roughly, of the patients, convenience is rated as the most likable thing of their schedule and that rises extremely high to when we get to 30-night continuous wear and we see a rating of over 85 percent.

[Slide.]

When asked about their overall satisfaction with the modality, 80 percent of our

patients rate their satisfaction when asked on a 1 to 100 scale where 100 indicates excellent satisfaction as over 85 percent.

[Slide.]

They also, when asked to rate various aspects of both convenience, safety, vision comfort and how their eyes appear, the appearance or lack of redness that is discernable with continuous wear, they all give very high satisfaction ratings for the performance of these lenses with this modality.

[Slide.]

We have also asked a group of patients that were previous daily wearers and have since moved to continuous wear to look back at their previous daily-wear experience and compare overall satisfaction, convenience, vision, comfort, comfort at end of day and just how clean their lenses feel. For all these attributes, the patients rate their overall satisfaction or their experience in continuous wear as being significantly better than their daily-wear experience.

[Slide.]

When we asked our patients what the disadvantages, if any, were of 30 nights and

wearing lenses on this schedule, 50 percent of our patients reported they saw no disadvantage in wearing lenses in this way. We still have the remaining problem, 13 percent rated dryness and discomfort.

[Slide.]

Having experienced extended wear or continuous wear for an average 27 months, the majority of the patients, now 92 percent, want to be able to sleep in their lenses either for continuous-wear purposes, and that is over, now, 70 percent of patients or at least on an extended-wear basis.

[Slide.]

In the studies that we conducted LVP and CCLRU, our patients are on a 30-night schedule. However, they are encouraged to remove their lenses for an overnight break or temporarily for a clean, rinse and reinsertion as needed. We also allow them to use unit-dose saline for morning and night if they wish.

When we look at the patient's success or their ability to be able to achieve 30 nights wear by looking at the number of nights of consecutive wear which they achieve, we see in 82 percent of

all visits, patients are able to wear their lenses consecutively for 28 to 30 nights and a further 12 percent are able to wear them for 21 to 28 nights without needing any removal.

[Slide.]

This data here is from the 12-month visit where we look at the percentage of patients who do not remove their lenses at all for an overnight schedule or an overnight removal outside their schedule. At this visit, 68 percent do not take their lenses out for an overnight break. 14 percent are taking them out once and a minor percentage are taking them out more than once for an overnight break during their 30-night schedule.

[Slide.]

As well as monitoring the number of overnight removals across time and, as you can see here, this does not change across the 30 months that we have monitored these patients and it averages that 71 percent of our patients are able to achieve 30 nights of continuous wear with no overall break.

We also rate, or collect information about how many times they temporarily remove their lenses for a quick rub and rinse as well as overnight

removal. Again, across this 30-month period, there is no change and it averages 53 percent that are not needing to take their lenses out at all during that period.

[Slide.]

Collectively, the CCLRU clinicians have been involved in development of extended wear and extended-wear research now for over 25 years not only with the conventional Dk materials, also with the high-Dk rigid materials as well as silicon elastomer and silicon hydrogels.

Despite this vast experience, we still, as clinicians, feel uncomfortable about using low-Dk extended wear even in the clinical trials that we conduct, and the reasons, primarily, are because of the problems with hypoxia, safety and infection and the concerns of ocular redness. It is for these reasons that we value the development of these new high-Dk materials.

[Slide.]

Our patients are very enthusiastic about both the convenience and freedom from spectacles that continuous wear offers. When we surveyed over 200 of our patients and asked, "Have you ever considered refractive surgery to permanently

correct your vision correction?" we found that 69 percent have.

[Slide.]

However, after they have worn continuous wear, 30 nights continuous wear, we ask again those 143 patients that had considered refractive surgery what they now prefer as a means of permanent vision correction. Now, only 39 percent of those original 143 patients are considering refractive surgery and the others are happy to remain with continuous wear as their vision correction option.

[Slide.]

So, in summary, I would just like to say that we believe the value and the worth of this development of continuous wear and high-Dk materials for our patients is that it offers a very convenient modality for permanent vision correction and for practitioners, the decreased hypoxic effect is, of course, of great interest to us.

Thank you.

DR. SUGAR: Thank you, Dr. Sweeney.

The next presentation will be by Dr. James Kerr.

DR. KERR: Good morning. I am in private optometric practice in Saskatoon, Saskatchewan,

Canada. I do not now work for Ciba Vision nor have I ever. They paid my way here, but I have no other financial interest in Ciba and they have had no input into my remarks.

They are based on my clinical experience with this product and that clinical experience began when I was involved in the Canadian clinical trials of the Focus Night and Day lens beginning in March of 1999. I fitted twelve patients according to that protocol which involved using a competitor's contact lens in one eye and the Focus Night and Day Lens in the other.

It became immediately obvious to me that this new product was superior to anything we had used before, so much so that at the conclusion of this study, all of the patients continued to wear the Focus Night and Day lens on a 30 day-and-night continuous-wear schedule.

The lens was then approved for 30-day continuous wear in Canada in June of 1999. Since that time, our office has ordered over 900 six-month supplies of this lens. This represents approximately 500 different patients. The majority of these patients wear the lens on a 30-day continuous-wear cycle.

Ciba then expanded the parameters of the lens in April of this year. Up until that time, the lens had one base curve and limited powers and that limited the fittings that we could do with this lens. When they expanded the parameters, we had a much wider range of fitting, much wider range of powers.

Since that time, the lens has simply taken off in our practice. We have five doctors prescribing it. All five are involved now. Something like 75 percent of our 14-day disposable lens wearers choose to switch to this lens when they are advised of the features and benefits of the lens.

Many, if not most, are skeptical partly because we have always discouraged extended wear and partly because most patients, in spite of our opposition to extended wear, they have either intentionally or otherwise slept with their lenses, convention lenses, and they find them to either stick or fog up or both. After learning that this new product does not do this, most patients are interested and, after a trial period of one month, they are usually very enthusiastic.

Our experience to date with this lens has

been as follows: the lenses are now very comfortable when they fit properly and, with only two base curves, there are limitations to the fitting. But we expect good comfort with the lens. We have seen no corneal edema at all. We have seen less surface deposition than most other lenses.

We have seen no neovascularization. Most patients find the lenses do not dry as much as other lenses. I have an asterisk here. I live in Saskatchewan which is something like the Sahara desert so most new products, most contact-lens products, if they are dry at all, we have big trouble with them. With this one, we have had no difficulty there at all.

I haven't seen, to this date, any lens stick to the cornea. Most patients wake in the morning and either blinking or installation of a wetting drop renders the lenses immediately comfortable. We expect less limbal injection and whiter eyes than any daily-wear lens presently available. I think you have seen reference to that. This is the third time in a row. These eyes are whiter than any product we have had before.

We have seen no giant papillary conjunctivitis to this point and we have seen no

cases of microbial keratitis or other significant infections. I, personally, have seen two patients develop a contact-lens-induced acute red eye. Both of these patients responded well to topical antibiotic steroid drops and were able to resume continuous wear of the contact lenses without any loss of vision or recurrence to this date.

Other complications have been minor but include lens coating, dryness, lens awareness and mucin balls. Our patients' acceptance of this lens has been a surprise to us. Because of previous product failures, there is a natural skepticism and resistance to the concept of continuous wear. But, as more and more patients are successful, the demand is truly amazing.

The benefits are obvious as it affords to patient who is handicapped by refractive error to live their lives in a less complicated way with far less risk of adverse events than any other form of correction.

This correction is adjustable so that as their eyes change, so can the correction. It is safe. It is reversible and the complications that do arise can be easily managed.

It is not without risk. I think it would

be unreasonable to expect that we will not see ocular infections, perhaps some serious ones. But it is risk management that we must consider.

We know these lenses pass more oxygen along the cornea to maintain its natural resistance to disease. We know that certain ocular pathogens do not adhere to the corneal epithelium and they do with conventional hydrogels. We know that decreasing chemical damage to the epithelium caused by current multipurpose solutions will increase the cornea's resistance to disease.

We know that compliance with current disposable protocols and cleaning protocols increases the likelihood of infection with conventional hydrogels. It is intuitive that such significant improvements will decrease the risk of ocular complications of contact-lens wear compared to current systems. This certainly seems to be born out in my clinical experience.

The real risk management, however, is in comparing 30-day continuous-wear Focus Night and Day lens to refractive surgery. I practice in a city that is well advanced in refractive surgery. We have three laser centers in a city of 200,000 people. Two have been operating for six years or

more and there is a very high public use of and demand for this form of continuous vision.

In my own practice, I have over 600 patients who have had refractive surgery and the results have been truly outstanding. But the statistics do hold out and, in my practice, I now have 18 to 20 patients who have had complications resulting in permanently reduced best corrected vision.

When this happens, it is, indeed, permanent and irreversible. Since the incorporation of the Focus Night and Day lens into my practice, I have gone from sending ten patients a month for refractive surgery to sending two patients a month. None of the patients who have chosen the contact-lens path have lost any vision and, indeed, we have been able to adjust their correction to provide optimum vision.

I feel that offering this alternative form of continuous wear has, therefore, resulted in me preventing vision loss in fifteen to twenty patients who may have otherwise have opted for refractive surgery while still providing them with continuous vision.

The Focus Night and Day lens is the first

real improvement we have had in contact-lens technology in over a decade. It has become an important tool in our practice and I expect its use to continue to grow to the point where we use this sort of product in every contact-lens application.

I also believe it gets us much closer to the point that when we remove a lens, we throw it away, whether it is a single-day, 30-day or, perhaps, some day, a year or more. Focus Night and Day lenses truly revolutionized our practice. We think it is a shame that this product is not yet available for citizens of this country.

Thank you.

DR. SUGAR: Thank you.

If any panelists have questions for the previous three presenters, we have a minute or two to allow that.

Seeing none, we will move on to the open committee discussion and the Division Update by Dr. Rosenthal.

Division Update

DR. ROSENTHAL: I just have one issue to announce to you, Mr. Chairman and Panel, and that is that Nancy Brogden, the Deputy Director of this Division, has been promoted to Director of the

Division of Diagnostic, Radiologic, Abdominal Devices. That includes the rest of the body except the eyes.

DR. SUGAR: And ears.

DR. ROSENTHAL: And ears, and nose and throat. David Whipple has been appointed the Deputy Director of our Division.

DR. SUGAR: Thank you.

We will now have the Branch updates. Dr. Beers.

Branch Updates

DR. BEERS: Good morning. I am Everette Beers. I am Acting Chief of Diagnostic and Surgical Devices Branch. There have been no personnel changes in the Branch since we updated last November. We have approved a PMA and cleared some 510(k)s.

I do want you to be aware that all approvals and clearances, additional information can be obtained on the FDA websit, fda.gov/cdrh. You have to figure it out yourself from there. Sometimes we can get there and sometimes we can't.

For PMA approvals, P930016, Supplement 12, VISX LASIK Hyperopic Astigmatism for up to 5.00 diopter sphere and up to 3.00 diopter cylinder was

approved April 27, this past April 27. That's all we had on PMA approvals.

For 510(k)s, I did want you to be aware of some of the 510(k)s. This panel does not see 510(k)s but those are our less risky devices but we frequently have very forward-looking and cutting-edge-technology types of devices in these areas that we call 510(k)s.

The first one is K01199 cleared in June 2001. That is the Bausch & Lomb Proview Eye Pressure Monitor, formerly the Fresco Phosphene Tonometer. It was cleared for over-the-counter home use. The tonometer is utilized on the closed eyelid and requires a subjective response of the perception of the phosphene which is placed on the eye, on the closed eye. When you see a phosphene, a little spring tells you what your eye pressure reading is.

Another one I wanted you to be aware, that we have put up on the CDRH website a Keratome LASIK Guidance. Previously, keratomes have not been allowed to state that they were for use with LASIK. Now, we are saying that it is allowed to say that the keratome can be used for LASIK. Keratomes are class I devices. Lasers are class III devices. It

gets all very confusing, but we have put a guidance up there that has changed previously when class I devices were not allowed to advertise or be indicated for class III indication of LASIK.

Finally, in the 510(k) area, wave-front analysis autorefractometers, or aberrometers, are exempt with limitations. Exemption means that you do not have to submit a 510(k) for these prior to marketing.

The product code for these devices is NCF. These exempt 510(k) devices do not have to submit premarket notification to FDA but, in accordance with Section 513(i)(1)(E) of the Food, Drug and Cosmetic Act, these exempt aberrometers must carry the warning in their labeling that the safety and effectiveness of using the data from this device, whatever it is, have not been established for determining treatments involving higher-order aberrations of the eye such as coma and spherical aberrations.

You can also see 510(k) K000637 for the limitations on this device. If you are not familiar with Wave Front autorefractometers, I think I mentioned in the handout for the open session a little bit more about these devices. In

general, they use a laser beam reflected from the retina to determine distortions through the entire visual system of the eye.

These aberrations include sphere, cylinder and axis and the higher-order aberrations such as coma and spherical aberrations. So they are used like regular refractometer to get your sphere, cylinder and axis. You can also get some other readings, but they are not allowed to use those to do those higher-order aberrations for refractive treatments.

Finally, I think most of you are aware of our LASIK websit, www.fda.gov/cdrh/lasik. We have had tens of thousands of hits on that website and we found that it has been very useful to consumers as well as many practitioners.

Finally, I know that some of you, as practitioners and also being on the panel, occasionally receive questions from consumers regarding something that is up with the FDA. You really should forward those consumer questions to the Office of Health and Industry Programs, the Division of Small Manufacturers Assistance, DSMA.

You can have them call 800 638-2041 or they can send in an e-mail request to

dsma@cdrh.fda.gov. That information should also be in the open session handout that is in your package.

Are there any questions?

DR. SUGAR: Go ahead, Marcia.

DR. YAROSS: Not a question, but I would really like to commend the agency on the guidance document on the LASIK indication for keratomes. I think that that was really the clearest application of least burdensome and I believe it is much appreciated.

DR. BEERS: Thank you.

DR. SUGAR: Thank you, Dr. Beers.

Now Donna Lochner will speak for the Intraocular and Corneal Implants Branch.

MS. LOCHNER: I would like to announce the PMA approvals since the last panel meeting. First, Staar Surgical P000026 AquaFlow Collagen Glaucoma Drainage Device, Model CGDD-20, was approved on July 12. This PMA was reviewed by the panel in November, 2000.

The next two PMAs were not reviewed by the panel because we felt that there were no new issues of safety and effectiveness presented. The first one, Pharmacia P990080 for the CeeOn Edge Foldable

UV-Absorbing PC IOL Model 911A was approved on April 5.

Last, Anika Therapeutics, P00046, which was a licensing PMA in which Bausch & Lomb provided reference rights to P810025 which is Amvisc sodium hyaluronate was approved April 18. This means that Anika has approval to distribute and manufacturer the Amvisc sodium hyaluronate under their label.

At this time, Anika did not request distribution under the Anika label. Instead, they received approval for Staar Surgical Company to distribute the product as Staarvisc II, sodium hyaluronate.

That concludes my updates.

DR. SUGAR: Thank you.

Next, Jim Saviola will talk on the Vitreoretinal and Extraocular Devices Branch.

DR. SAVIOLA: Thank you, Dr. Sugar. Good morning, everybody. There are a few clearances and PMA approvals that I wanted to inform you about this morning. I had neglected in my prepared remarks to mention a website that we were involved in developing recently. I thank Dr. Beers for jarring my memory on that.

About two months ago, there was a website

posted on the Center web that addresses questions and answers regarding purchasing contact lenses from the Internet or from other sources other than from an eye-care practitioner. That is something that we developed in response to inquiries we were getting regarding prescription dispensing and things of that nature. So if people are interested in that, I would refer you to our website for that.

In the class II area for 510(k) clearances, the first area I would like to discuss is orthokeratology lens clearances. On February 28, 2001, we cleared the Paragon Fluroperm 151 for daily-wear orthokeratology. That K number was 010109. The labeling for that product includes reference to a previous Paragon study involving the Fluroperm 60 material, so that is where that data came from for that new clearance.

Polymer Technology received a clearance for the Polymer Tech Boston EO lens and also for the Polymer Tech Boston Equalens II, both on February 16. Those K numbers are K003932 and 3933. Those two had included references to the Contex AirPerm clinical study that was conducted by Contex.

Polymer had also received a clearance for

their XO material back in August of 2000. So, with all these new clearances, there are now a total of six orthokeratology lenses cleared. As you see, some of them are based on original clinical studies such as the Context AirPerm and also the Paragon Fluroperm 60. Others are using data as a reference within the context of determining equivalency and being able to do that in class II which is something you can't really do in class III.

In the lens-care product area, I told you last meeting about Opti-Free EXPRESS Multi-Purpose Disinfecting Solution manufactured by Alcon and how they received a clearance for the No-Rub care directions. Their first clearance was in July, 2000. Those are for lenses replaced for 30 days or less followed by a second clearance in October of 2000 to remove the 30-day limitation to include soft lenses prescribed on any replacement schedule.

We now have two more care products that have received a "no-rub" clearance for lenses replaced 30 days or less. K003252 cleared on February 21 for Allergan Complete Multipurpose solution and K003345 cleared March 26 for Ciba Vision's AO Sept One-Care peroxide solution which has a surfactant added to the peroxide.

With all of these clearances, there is still wording in the labeling to advise users that additional products or procedures such as rubbing their lenses may be recommended by the eye-care practitioner.

In the class II area, I had one PMA to inform you of, and that is Vistakon (lenefilcon a) soft hydrophilic contact lens which was approved on February 16, 2001. That is now indicated for daily wear and for extended wear up to seven days. As Everette mentioned, some of these products are not reviewed by the panel and seven-day extended lenses are one of those that, in class III, we do not refer for panel recommendation and review.

I neglected to report down the PMA number for that, so if anybody is curious, I can ask Stan Rakowsky or any of the other representatives of Vistakon in the audience this morning.

Thank you very much.

DR. SUGAR: Thank you. Are there any questions from the panel of the Division Chiefs? Branch Chiefs; sorry. Sorry for the promotion.

Dr. Pulido?

DR. PULIDO: Dr. Saviola, have any of the orthokeratology lenses come before panel?

DR. SAVIOLA: Not for the daily-wear indication. For extended wear, overnight wear, we plan to take those, at least the first one, for panel.

DR. SUGAR: Dr. Yaross.

DR. YAROSS: I did have one question for Ms. Lochner. Can you provide an update on the status of the reevaluation of the age indications for IOLs?

MS. LOCHNER: For those that may not know about this issue, FDA has been doing basically -- we have been doing some research, basically a metaanalysis of the literature as well as working with Dr. Apple's group on postmortem globes with the Academy on their outcomes base to compile data to present a case for lowering the age indication for IOLs to adults instead of age 60 and over.

We have actually completed substantially the body of the work, the actual analysis, and this is being prepared in the hopes of publication. Right now, this publication, this draft publication, is being reviewed by the authors within FDA, the Academy and Dr. Apple's group to follow.

Then we plan to submit this article for

publication. It is our hope that once this article is published, sponsors could use this as a reference of valid safety and effectiveness data to support a lowered age indication.

So, in summary, the article has been drafted. It is in the "being-reviewed" stage prior to publication.

DR. YAROSS: Thank you.

DR. SUGAR: Jim?

DR. SAVIOLA: There was another answer I forgot to give, too, Dr. Pulido. The very first ortho-K lens we had for Contex we did refer out for panel homework assignment to one of the panel members.

DR. BEERS: Regarding the LASIK indication for keratomes, I should mention that the keratomes must meet certain requirements before they are allowed to use that LASIK indication. So you should look at the website at that guidance to determine whether or not their keratome meets those requirements.

DR. SUGAR: Thank you, Chiefs.

PMA P010019

We are now going to move on to the discussion of the PMA at hand today, PMA P010019.

This will begin with a one-hour presentation by the sponsor. I would like to remind everybody to state their name before speaking so that the scribes can have this in the transcript.

MS. PLESNARSKI: Good morning.

[Slide.]

My name is Alicia Plesnarski. I am a regulatory specialist in the Global Regulatory Affairs Group of Ciba Vision Corporation. I have been with the company for about ten years and, for most of that time, I have been the regulatory project leader on the project team for the PMA device.

Today, I am very proud and excited to be here as part of this team. We are here to present and discuss Ciba Vision's PMA P010019 for See3 (lotrafilcon A) Soft Contact Lenses with an indication for up to 30-night extended wear.

[Slide.]

My presentation will be brief. I will talk a little bit about our company and the PMA device and then introduce the rest of the team.

First of all, Ciba Vision is a eye-care unit of Novartis. We began as a small start-up company in 1980 and have grown into a global

corporation involved in research and development, manufacturing and marketing of ophthalmic products. Our corporate headquarters are located in the suburbs of Atlanta, Georgia and today our company makes and markets contact lenses, lens-care products and intraocular lenses and we maintain FDA-registered manufacturing facilities on three continents.

[Slide.]

Regarding the PMA device under consideration today, the See3 lotrafilcon A soft contact lens for up to 30-night extended wear is classified as a class III medical device. The lens material, lotrafilcon A, is a 24 percent water, 76 percent fluorosilicon-containing hydrogel which is surface treated.

As a low water, nonionic polymer, this lens material falls into FDA group 1 and, while the lens has many physical and optical characteristics that are similar to other soft contact lenses, one extraordinary feature of this lens material is that it has oxygen permeability of 140 delivering an oxygen transmissibility of about 175 for a -3.00 diopter lens with a center thickness of 80 microns.

[Slide.]

To date, the lenses haven't been marketed in the U.S. Ciba Vision has obtained FDA 510(k) daily-wear marketing clearance in May of 1997. Outside the U.S., the lenses are marketed under the trade name Focus Night and Day in product packaging that bears the CE mark.

In early 1999, a global market introduction began and the product was launched in many countries in the European Union, in Canada and in Australia. Today, the lens has over 250,000 wearers in over 40 countries.

[Slide.]

Now, while soft contact lenses have been on the market for over thirty years, much of the exciting advancement in contact-lens material properties has occurred more recently. The early '90's marked the beginnings of a strong commitment and targeted initiatives by industry to develop 30-night continuous wear as a safe and effective vision-correction option.

In terms of research and development of next-generation contact-lens materials, the progress in this area can be followed in the dozens of scientific articles published in professional journals regarding high-Dk lenses and extended

wear.

[Slide.]

Regarding our PMA and development of the SEE3 soft contact lens, this project was initiated in the early '90's and our goal was to develop and market a noninvasive, safe and effective and convenient 30-night extended-wear soft contact lens. We are talking now of a period of about ten years and, over the course of lens development, there have also been some significant developments in the regulatory area for medical devices.

With passage of the Medical Devices Directives and CE marketing requirements in the European Union and revision to the FDA GMP Regulation to include design controls, the SEE3 lotrafilcon A lens became one of our first projects to proceed under a formalized design-control system compliant to both the FDA quality-system regulation and ISO 9001 Quality Systems requirements for design controls.

Before we move ahead, I wanted to mention some commonly used terms you will be hearing this morning. SEE3, lotrafilcon A and Focus Night and Day are the project name, lens material name and trade name for the contact lenses. The phrases

extended wear and continuous wear may be used interchangeably and we mean no differences in these phrases.

[Slide.]

In just a moment, we are going to be moving on to the clinical findings, but I did want to mention the lens has undergone a comprehensive series of nonclinical testing to support product safety. Some of those tests are listed on the slide, but the actual list of testing exceeds those recommended by the FDA in 1989 and 1994, Contact Lens Guidance Documents and includes additional physical-chemical testing, biocompatability studies as well as analysis of worn lenses.

Wherever possible, the methods conformed to the applicable ISO or ANSI standards for contact-lens testing.

[Slide.]

The important findings from all nonclinical testing are that the lenses are nontoxic and biocompatable. They are stable and compatible with lens-care solutions. They have material properties which are consistent with or better than other soft contact lenses and these properties remain unchanged after lens wear.

The results of all nonclinical tests support the safety of lotrafilcon A lenses for their intended use.

[Slide.]

At this point, I would like to introduce the rest of our team. Presenting today, and up next, will be Dr. John McNally who will provide information on the clinical study design and results. After John, Dr. Scott Robirds will talk about product labeling and our proposed postmarket study protocol.

[Slide.]

Also with us today and available to help with questions and other information are Dr. Curtis McKenney from our Research Clinic who has been on the SEE3 project since its beginnings and Dr. Gary Cutter, a biostatistician who worked with us on a consultant basis regarding study design and statistical analysis.

In addition, the president of our lens business, Stuart Heap, is also here with us today. On behalf of Ciba Vision, Stuart authorized payment of our travel expenses to Washington and we are hopeful he is going to do the same for our return tickets back to Atlanta this afternoon. Stuart

will have some closing remarks later today.

That concludes my presentation and I thank you for your time and attention. Up next, Dr. John McNally.

DR. McNROBALLY: Thank you, Alicia.

[Slide.]

Good morning. My name is John McNally. Today, I have the pleasure of presenting the culmination of over a decade of extended-wear research carried out by many hands from around the world. I started my own interest in extended-wear research some twenty-five years ago in the laboratories of Dr. Mandell at U.C. Berkeley School of Optometry.

I have since been with Ciba Vision for twenty years, continuous and extended years I might say, serving in various clinical, regulatory and research management positions. I am currently the head of continuous-wear research programs.

[Slide.]

This morning, I will briefly touch on some of the background information regarding the product. Then I will provide an overview of the results of the clinical trial and provide some comments in response to questions we have received

from the reviewers thus far.

[Slide.]

Here, I would like to reemphasize three of the distinguishing properties of the lens material that may be of importance for our discussions this morning. Of course, the high oxygen permeability, the low water content, the nonionic nature of the material and the modulus which, for the panel's reference, is higher than many soft lenses on the market but is not unlike a number of contact lenses that have been on the market for many years.

[Slide.]

The oxygen permeability of lotrafilcon A is due to the siloxane content of the market. Unlike hemabased hydrogels which require increases in the water content to increase the oxygen permeability, as shown in the curve on the bottom of this illustration, it is obvious to see that the lotrafilcon A polymer, shown here in the upper left quadrant of the graph, is a departure from that principle and a clear breakthrough in terms of oxygen permeability.

[Slide.]

Critical to the unique nature and performance of this polymer as well was the

discovery of the requirement for a continuous hydrogel phase allowing the movement of ions through the lens which is then responsible for or related to the lens movement and the maintenance of ion mobility. We have included a paper describing this work in your panel packet.

[Slide.]

In the early phases of clinical development, we studied several of the important performance outcomes required for successful extended wear, namely overnight corneal swelling, bacterial colonization, lens-surface cleanliness. In the panel packet, we have included summaries of this work or published articles, when available.

I will briefly review the results of these three.

[Slide.]

In a study of overnight corneal swelling published by Fonn and coworkers, the SEE3 lens produced a mean corneal swelling of 2.7 percent overnight compared to 8.7 percent for the Acuvue control clearly demonstrating one advantage of the increased oxygen transmissibility.

[Slide.]

In a study of bacterial colonization of

the lenses during wear published by Keay and coworkers, SEE3 lenses were aseptically removed from the eye after 30 nights of continuous wear and compared to Acuvue lenses sampled after six nights of continuous wear. There were no significant differences in the number of sterile samples, as shown here, nor in the amount of types of bacteria found, thereby showing no increased bacterial colonization over the 30-day period.

[Slide.]

In a clinical study conducted at Ciba Vision, lenses were retrieved for analysis of protein buildup. SEE3 lenses were retrieved after 30 nights of continuous wear and Acuvue lenses after six nights of continuous wear.

In this and similar studies, the SEE3 lens made of the nonionic lotrafilcon polymer shows remarkably less protein buildup than the control lens, in this case that of lotrafilcon which is an ionic polymer.

[Slide.]

After these early studies and prior to the launch of the product in 1999, we completed an international safety and effectiveness trial. The rates of adverse events in that trial are presented

here. No statistical difference was found between the SEE3 lens after 30 nights of continuous wear and the control lens, Acuvue, at six nights of continuous wear.

These rates for adverse events are similar to the rates found in the U.S. trial that I will discuss in just a few minutes.

[Slide.]

As you have heard, we launched the product internationally in 1999 and currently there are approximately 2.5 million lenses in the marketplace. From that, we estimate that we have approximately 250,000 wearers representing a cumulative experience of approximately 100,000 patient years.

These numbers are updated from those included in your packet and these are the current numbers and represent our best knowledge. We have had five cases of potential infectious keratitis reported to us. I use the word "potential" because of differing definitions by practitioners around the world. But, nonetheless, these were severe adverse events.

Based upon this information, our best estimate for infectious keratitis is 5 in 100,000

patient years although we realize that this will not hold up to epidemiological scrutiny.

Earlier this year, we added a second base curve based upon feedback from the marketplace as well as our findings in our clinical trials. We also added plus lenses and high minus lenses at the same time.

[Slide.]

Overall, feedback from the international marketplace has found the Focus Night and Day product to offer a desirable alternative for those seeking the convenience of around-the-clock vision correction.

We have also had numerous anecdotal reports of less dryness and less redness from wearers. The lens offers flexibility both in terms of wearing regimen as well as the ability to easily adjust refractive correction as required and it has been particularly well received in the higher refractive powers.

[Slide.]

So now to the results of the safety and effectiveness study in the United States. After briefly reviewing the study design, I will present the key results and the conclusions and some

elements of clarification required to address the reviewer's questions that we have received.

The evidence presented in the PMA packet is in support of the indications being sought, in particular the wearing schedule indication of up to 30 nights of continuous wear and the reduction in contact-lens dryness symptoms.

[Slide.]

The objective of the study was stated as follows: to determine whether the SEE3 lens when worn for up to one month extended wear and replaced on a monthly basis performed as well as the Acuvue control lens when worn for up to one week extended wear and replaced on a weekly basis.

[Slide.]

This was one of the largest prospective contact-lens studies conducted to date in support of safety and effectiveness. It was a one-year open-label randomized controlled clinical trial involving 59 investigative sites. As I mentioned, there were differences in both the wearing schedule and replacement frequency with SEE3 being worn for up to a month extended wear and replaced monthly and the control lens weekly extended wear and replaced weekly.

Additionally, during the study, the SEE3 lens was available in a single base curve whereas the control lens was available in multiple base curves.

[Slide.]

The primary safety endpoint was infiltrates of grade 3 or greater or any infiltrates with overlying fluorescein staining. This is a conservative endpoint as contact-lens infiltrates are not usually infectious in nature and rarely lead to reduction in visual acuity. However, this endpoint may serve as a threshold surrogate for an infectious ulcerative keratitis or, as it is commonly referred to in the contact-lens industry, microbial keratitis.

Microbial keratitis is a rare corneal complication and is therefore prohibitive to study in a premarket trial and is better suited to postmarket evaluation such as we will propose later.

[Slide.]

The primary effectiveness endpoints were the visual acuity and the wearing time achieved with the contact lenses.

[Slide.]

The sample size for the study was based upon a noninferiority statistical design. This type of design allowed us to test at the alpha 0.05 level whether the SEE3 lens was worse than the control by a specified amount referred to as the equivalence margin.

For the safety endpoint just discussed, the equivalence margin was set at 5 percent and the estimated endpoint rates were set at 8.6 percent for reasons discussed in the clinical protocol and report that you have received.

A noninferiority study design has the advantage that we specifically set out to prove that you are not different by a certain amount unlike the statistical outcome from many studies where equivalence is claimed because a difference wasn't detected.

The null hypothesis, then, is that the rates are different by 5 percent or more and noninferiority would be demonstrated by statistically rejecting this null hypothesis. Although this study design preceded the draft FDA extended-wear guidance for extended-wear lenses, it closely aligns with the statistical principles in that guidance and the examples provided as well.

[Slide.]

Under these assumptions just discussed, the sample size at 80 percent power would be 389 subjects per group. In order to have greater than 80 percent power, we increased our sample size to 500. This provided us a robust study design that would provide 87 percent power at the estimated rate of 8.6 percent as shown on this graph.

It also would provide adequate power across a wide range of potential outcomes as shown here. We were also satisfied at the gut-feel clinician level with the maximum SEE3 rate we might observe in the trial, shown in the bottom row, and still reject the null hypothesis.

[Slide.]

Our final enrollment target was set at 700. We included a 15 percent allowance for the possible inability to fit all subjects with a single base-curve parameter in the SEE3 product and made a further 20 percent adjustment for dropouts that may occur over a year's period of observation.

[Slide.]

So, to the results. Today, I will discuss the enrollment and the accountability, the discontinuations, the primary safety endpoint and

adverse events and the effectiveness endpoints of visual acuity and wearing time and the results regarding contact-lens dryness.

[Slide.]

697 SEE3 and 698 control subjects were enrolled. 39 SEE3 and 17 control subjects were unable to be dispensed. The difference between the two here is due to 20 SEE3 subjects that did not achieve an acceptable fit at this time. In total, 658 SEE3 eyes and 681 control eyes were dispensed equating to 1,316 and 1,362 eyes, respectively.

[Slide.]

The demographics were representative of the contact-lens-seeking population and the two groups were nearly identical. Subjects were actually dispensed in the power ranges you see listed here, +6.00 to -6.00 for SEE3 and +4.50 to -6.50 for Acuvue. Approximately 95 percent of the subjects in each group were myopic, as is typical of the current contact-lens-wearing population.

[Slide.]

The groups were also well matched in terms of previous contact-lens-wear experience as shown in this chart. It is important to note that approximately 60 percent of the subjects were new

to extended wear and, thus, were not established veterans.

[Slide.]

A larger proportion of the SEE3 group, 175 versus 102, were discontinued from the study, many for reasons we had foreseen, as I will discuss next. Accountability was excellent in the study with complete data available on 96 percent of the subjects' dispensed lenses.

[Slide.]

The four biggest differences and reasons for discontinuations are seen here; discomfort, lens fit, biomicroscopy and acuity with contact lenses. Let me discuss each one of these separately.

[Slide.]

The difference in discontinuations for discomfort was largely driven by the difference in the first week and overall in the first month. After the first month, the rates were similar, as you can see graphically depicted on the bottom of the slide.

[Slide.]

The same is true for discontinuations for lens fit, as you can see in the chart, and again in

the graph at the bottom. All but one of the SEE3 discontinuations for lens fit were due to unacceptably flat or loose-fitting lenses.

[Slide.]

Discomfort and fit discontinuations are very likely related. With the SEE3 lens, when the lens is too flat relative to the cornea, the lens edge will lift or even buckle, as you see here. This, of course, is an extreme case and this subject would likely have been discontinued for lens fit.

However, when the edge lift is more subtle or sporadic, then it may not be observed by the investigator during biomicroscopy but is evident to the wearer by lid sensation or discomfort at the area of edge lift. We have addressed this both in the fitting guide, as Dr. Robirds will explain, and in a subsequent development of a second base curve.

[Slide.]

In response to reviewer questions, we examined various factors concerning the discomfort discontinuations. We found no correlation to corneal curvature, refractive power or lens fit with only a very slight trend towards steeper corneas and towards higher myopia. This lack of

correlation can perhaps be explained by the fact that, on the steepest corneas, the lens fit was obviously flat and these subjects were discontinued for lens fit.

This would leave, then, only a trend for these other factors as they relate to discomfort discontinuations.

[Slide.]

Reviewers were also interested in the investigators' decisions to discontinue subjects for biomicroscopy and especially asked about the severity of the findings. Four SEE3 subjects were discontinued at the first event, one subject for a peripheral ulcer or CLPU in the second week of continuous wear with the infiltrate and staining grades as shown here.

Two of these subjects were discontinued for infiltrative keratitis, where I have IK listed, because the event occurred in the first month of wear and the investigator recommended against continuing. One subject with a previous history of Thygeson's was discontinued shortly into the study due to a reoccurrence felt by the investigator to be unrelated to the product.

Three subjects were discontinued because

the event listed in the table in your report was their second event. One was a peripheral ulcer and two with infiltrative keratitis. The other discontinuations for biomicroscopy were four with papillary conjunctivitis, three of the four from one investigative site, and all subjects with previous history of papillary conjunctivitis, and five other subjects for early microacyst rebound or dimple veiling.

[Slide.]

Two control subjects discontinued for events because they occurred in the second week, one for infiltrative keratitis and one for herpes keratitis. This latter was listed in the report table as intraepithelial keratitis. One subject was discontinued at the second occurrence of episcleritis and one additional control subject, with a peripheral ulcer, was discontinued for "other ulcer" and more appropriately should have been included in this listing.

[Slide.]

Several questions were raised regarding discontinuations for contact-lens acuity. As mentioned in the report, we encountered an issue in our packaging design causing a small percentage of

lenses to adhere to the package, thus distorting the optics as you see here in this photo. Although we adjusted the packaging design, we did not replace the clinical inventory.

All of the discontinuations for acuity were in the first three months of the study. After that, if a wearer experienced substandard vision when they put in a new lens, they simply replaced it with another one from the pack.

A question was also asked about engraving and deposits and I will address that at this time since you can see that the lens is engraved in this photograph. The surface treatment of the lens is applied after the engraving and, therefore, the engraving presents no problems for tear-film deposits.

[Slide.]

So, as I have explained, we found that the majority of the differences in discontinuations occurred in the first month and many for the fit reasons we had foreseen. We have provided guidance for this in the labeling as we will discuss.

[Slide.]

Now the results regarding the primary safety endpoint.

[Slide.]

3.1 percent of the control group and 5 percent of the SEE3 group experienced an endpoint infiltrate. You remember this is infiltrates grade 3 or greater or infiltrates with any overlying staining. These unadjusted rates were not statistical different.

[Slide.]

From these rates, we performed a survival or life-table analysis that would account for all subjects' time in the study and allow us to better estimate annualized rates for the safety endpoint. This life-table graph is in the report and shows the survivors or, as we say, those not voted off the island for experiencing an endpoint infiltrate.

[Slide.]

From that analysis, we obtained the estimated annualized rates of 3.3 percent for the control and 6.1 percent for the SEE3 lens. As pointed out in the report, this is a conservative estimate for the control rate since two control peripheral ulcers were not included in this statistical analysis.

One ulcer occurred at six months but was treated by a non-study ophthalmologist over the

holiday season. The ulcer was later confirmed by the investigator by the presence of a corneal scar. However, since no data regarding the infiltrate, itself, was provided, we did not include this subject in this calculation.

A second ulcer was seen in another subject in the control group at the 12-months visit. However, since the visit occurred at 378 days, including it in the life-table analysis would greatly overestimate the control rate since so few subjects were still in the study at that time, at 378 days.

Still, based on the noninferiority test I outlined earlier in this presentation, we calculate the p-value to be 0.0465 allowing us to reject the null hypothesis and demonstrate noninferiority.

[Slide.]

In response to the reviewers' questions, we examined various factors concerning the incidence of endpoint infiltrates. We found no correlation to refractive power, corneal curvature or lens fit.

[Slide.]

In the clinical report, we characterized the endpoint and analyzed various risk factors. I

note here only a few observations. The infiltrates were mostly paracentral and limbal and few were central. Subjects with a history of a previous event were at a higher risk for having an event and there was a trend for a higher rate in smokers although it was not statistically significant in our study.

[Slide.]

Our findings, then, in the primary safety endpoint were as follows: SEE3 was found to be noninferior to the control by the equivalence margin defined in advance and no subjects lost best corrected acuity with any endpoint infiltrate. We will provide guidance from our findings in the labeling.

[Slide.]

Now I will briefly cover overall adverse-event rates and discuss other eyes that required treatment during the course of the study. The primary safety endpoints just discussed were all considered adverse events and thus are also included in the overall rates that follow.

[Slide.]

In line with the draft guidance for extended-wear lenses, we classified adverse events

as serious, significant or nonsignificant using examples provided in that guidance. Roughly, these categories can be thought of as follows: serious adverse events are potentially sight-threatening events. For contact lenses, this would be optical axis or infectious ulcers. Based on the guidance, we also included any events in this category that had the presence of any anterior chamber reaction.

Significant events are not directly sight threatening but are usually treated to preclude potential escalation or other sequelae. Nonsignificant events are those that are typically managed through temporary removals of the lens or other palliative procedures.

[Slide.]

It is probably most meaningful to look at the cumulative rates. The rates are listed on this chart with the cumulative rate, shown on the bottom, being 9.4 percent for SEE3 and 8.3 percent for the control. If you remember, these rates were very similar to those that I presented earlier for the international safety and effectiveness trial.

Neither this cumulative rate nor any of the rates shown here were statistical different. Further details regarding events were included in

the report in the panel packet.

[Slide.]

In summary, regarding adverse events, we found no difference in incidence between the two groups, no cases of microbial keratitis and no loss of best-corrected visual acuity. The rates of these events will be provided in the labeling.

[Slide.]

A statistical difference was found in the proportion of eyes requiring management for contact-lens-induced papillary conjunctivitis or CLPC on this chart. For the SEE3 subjects, 1 of the 59 investigative sites reported 7 of the 30 papillary conjunctivitis subjects. All of these seven had had a previous history or CLPC.

[Slide.]

We found no correlation with surface deposits, lens fit, corneal curvature or refractive power. However, the location in the early onset in the SEE3 group suggest a possible mechanical origin for these cases. Subjects with a previous history of papillary conjunctivitis were at higher risk in this trial and, in the labeling, we addressed the potential increased risk of CLPC.

[Slide.]

Now I will discuss the primary effectiveness endpoints.

[Slide.]

The visual acuity results can be summarized as shown here. I have already mentioned the best-corrected visual-acuity results. The visual acuity with contact lenses worn remained within two lines of baseline for 98 percent of the evaluations over the course of the study. 83 percent of these evaluations were 20/20 or better and, although not shown here, 99 percent were 20/30 or better.

In approximately 90 percent of the evaluations, subjects rated the vision 8 or higher on a 10-point scale.

[Slide.]

We evaluated wearing time in several ways. First, we collected the prescribed wearing time. This was the wear schedule assigned by the investigator based on the case history and clinical findings for each subject throughout the course of the study and this was recorded at each visit.

Next, with the assistance of a diary, we also collected data from the subjects about the time of each removal and the reasons for that

removal. In this section, I will also address a question from the reviewers regarding the relationship of wearing time to adverse events.

[Slide.]

Here I think it is best to summarize the results first since some clarification is needed based upon review comments. Regarding the prescribed wearing time, no subjects were permanently prescribed less than a full indication in either group. However, prescribed wearing times were temporarily reduced in order to manage signs or symptoms.

[Slide.]

Two tables about prescribed wearing time were included in the text and I will briefly explain the data from the one-month visit table. This table shows 91.2 percent of the SEE3 subjects and 93.9 percent of the control subjects were assigned the full indication at this one-month visit. The remaining subjects were temporarily assigned shorter wearing schedules to manage whatever was happening at that particular time.

Over the course of the study, the prescribed wearing time at scheduled visits was at full indication for more than 90 percent of the

subjects in the study at the time of the visit.

[Slide.]

From the subjects, we learned that lenses were removed overnight for a variety of reasons including, of course, the scheduled removal but also for symptoms or problems the subject was experiencing or as needed for sickness or other demands in their life. The average wearing time was based upon the period between overnight removals.

[Slide.]

Although not highlighted in the text, Table 13A and 13B, the trend analysis profile, recorded the average wearing time over the course of the study. You can see that after the first month, the average wearing time for SEE3 was 26 to 27 days which consisted primarily of many subjects at 30 nights and a smaller group temporarily at shorter times.

[Slide.]

This chart presented in the report is a compilation of all reported wearing intervals from all subjects, and this includes months 1 through 12. For the completed subjects, 67.2 percent represents the percentage of time the 22 to 31 was recorded as the maximum wearing time in a month.

Over the course of a year, a single subject may be counted in several different categories on this chart depending on how they were wearing the lenses in that month.

Remember that all subjects wore the lens for full indication except for temporary periods. Basically, 67.2 represents the overall patient months on the completed subjects recorded at 22 to 31 nights and 88.1 percent represents the number of patient months at continuous intervals greater than seven months.

As you would expect, in the discontinued group, the wearing times were not as long since they were having difficulties with the lenses and ultimately discontinued. There may be alternative ways of representing the wearing time data in the labeling that the panel may prefer.

[Slide.]

We were asked to evaluate the relationship between wearing time and adverse events for the SEE3 lenses. This study design does not allow us to do that in a direct dose-response fashion since we did not have groups assigned at various wearing schedules. Remember that over 90 percent were described at the full indication over the course of

the study.

However, to address the root concern of the question, we looked at our data in several different ways. We calculated, for each subject, their own individual average of reported consecutive nights slept in the lens and looked for a relationship between this and adverse events. We found no increased risk with the increased average consecutive nights slept in the lens.

We also looked at the consecutive months of 30-night wear prior to the event; that is, whether the subject had worn the lenses for one or two or ten consecutive months of the 30-night regimen. Here we also found an increased risk for the increasing months at the full indication.

Finally, we looked at the consecutive days of wear in a given lens at the time of the event; that is, whether the lens had been worn for five or ten or 20 consecutive nights at the time of the event and we also found no increased risk with increasing nights of continuous wear of a given lens.

[Slide.]

We also summarized the reasons for the shorter wearing time reported by the subjects. In

addition to the temporary reductions prescribed by the investigators, the reasons for unscheduled overnight removals were summarized in table 25 and 26 and temporary daytime removals in tables 27 and 28.

For both groups, the main reasons for unscheduled overnight removals were eyes needed rest, irritation or allergy. For daytime removals, for both the test and control group, the main reasons were to clean or for irritation or for dryness. The multiple other reasons are listed in the tables in your report.

[Slide.]

In summary on wearing time, the prescribed and reported wearing schedules were predominantly the full indication. Symptoms, problems or lifestyle needs led to a temporary reduction in wearing time and, as analyzed in the SEE3 group, we were unable to show evidence of increased adverse events with increased wearing time.

[Slide.]

As the final part of my section, I will present the results supporting the finding of less contact-lens-induced dryness. This finding was supported by data gathered in the case history, in

the subjective questionnaires as well as the other subject diaries.

[Slide.]

Text table 19 in the report showed the symptoms reported to the investigator at each visit. While dryness remains the most often reported symptom in both groups, we found a statistically relevant decrease in the reported symptoms of dryness with SEE3 in both the completed and discontinued subjects which you see highlighted here.

[Slide.]

In the subject questionnaire, we also had statistically fewer reports of dryness upon awakening with the SEE3 lens. I have graphically represented the data from all patients presented in table 17A through D of the report and you can clearly see the shift towards less problems with dryness.

[Slide.]

Finally, and probably most important of the three, in the completed subjects, we found fewer unscheduled overnight removals for reasons of dryness in the SEE3 group compared to the control group as now highlighted here in the text table 25.

This difference was statistically significant with p equals 0.02.

[Slide.]

Based upon the consistency of these findings from three different sources, the SEE3 lenses demonstrated reduced dryness symptoms compared to the control. This is consistent with our international experience as well.

[Slide.]

So, as my concluding slide, we feel that the scientific evidence presented in this PMA application provides reasonable assurance that safety and effectiveness have been demonstrated for the requested indications.

[Slide.]

I will now turn the presentation to Dr. Scott Robirds who will discuss the proposed labeling and the postmarket protocol.

Thank you.

DR. ROBIRDS: Thanks, John.

[Slide.]

Good morning. I head up the Global Clinical Affairs Group at Ciba Vision. I have had the pleasure of working in clinical research and regulatory affairs at Ciba for the past fifteen

years. Prior to working at Ciba, I was an associate in a contact-lens practice for three years. That is as far back as I care to go.

I will be presenting a proposed product labeling and a summary of the postapproval study for the SEE3 PMA.

[Slide.]

I will start with the product labeling. As many of you know, the FDA has provided the contact-lens industry with guidance documents that provide helpful direction related to product labeling. The guidance for package inserts, practitioner fitting guide and patient instruction booklet are very comprehensive and the majority of the proposed labeling for the SEE3 product is consistent with these guidance documents.

So I am just going to focus on the elements of the proposed labeling that are unique to our product and, in some cases, are a departure from the published FDA guidance for contact-lens labeling.

As you can see here, the product name is Focus Night and Day and the product description portion of the labeling, a summary of lens properties, is presented. This is the same

information presented earlier by Ms. Plesnarski.

[Slide.]

The product description also includes the proposed approval range of lens parameters and the parameters that will be initially available. You can see the available parameters are a diameter of 13.8, base curves of 8.4 and 8.6, and powers will range from +6.00 to -10.00 in either quarter or half steps dependent upon the power selected.

[Slide.]

All of this information will be present in the package insert. The practitioner fitting guide will present only the available lens parameters seen here in gold.

[Slide.]

There are four indication statements that were submitted with the proposed labeling. I will just go through these. The first one is fairly straightforward and deals with vision correction and states that, "Focus Night and Day soft contact lenses are indicated for the optical correction of refracted ametropia in phakic or aphakic persons with nondiseased eyes with up to approximately 1.50 diopters of astigmatism."

[Slide.]

The second relates to wearing time. Here we stated that, "Focus Night and Day may be worn for daily or extended wear for up to 30 nights as recommended by the eye-care professional."

[Slide.]

The third indication relates to replacement intervals and lens-care systems. Here we say that, "Lenses should be replaced every month and when removed between replacements must be cleaned and disinfected with a chemical disinfecting system before reinsertion."

[Slide.]

The fourth indication states that, "Focus Night and Day lenses may reduce dryness symptoms that are present with regular hydrogel soft lenses." This claim is driven by findings in our FDA study as presented earlier by Dr. McNally.

In the reviewers' comments, there was a concern that this claim may be interpreted as being applicable for use with patients having aqueous tear deficiency or other pathological dry-eye conditions. Our intent was not to claim an indication of dry-eye relief in patients with pathological dry eyes but to claim a reduction in dryness symptoms secondary to routine contact-lens

wear. However, we acknowledge that we should clarify this in the language of the claim.

Another review commented that since our testing was confined to only one type of control lens, the data could not support such a broad claim for all regular hydrogen soft lenses. This is a valid comment and the claim should be modified to account for this.

[Slide.]

In the warning section, a portion of the standard language about ulcerative keratitis has been deleted, as you can see here. Our rationale for deleting this section is that we have not found this wording to be fully applicable to Focus Night and Day as we have just heard in Dr. McNally's presentation.

We would propose adding a statement such as, "The incidence of microbial keratitis with extended-wear lenses is approximately 20 per 10,000," or, alternatively, "Not all individuals can wear lenses for up to 30 nights continuously. Individual wearing times should be determined in consultation with your eye-care practitioner."

We believe these types of statements would address one of the reviewer's requests that a

statement be added that not all patients can tolerate continuous wear.

[Slide.]

In the precaution section, we have added three statements that relate to suitability as a contact-lens candidate. The added text is seen here in yellow. These precautions are added to the standard contact-lens labeling as a result of our FDA trial and relate to patients with a history of acute inflammatory reactions, giant papillary conjunctivitis or ocular allergies.

Subjects with histories of these conditions were at a higher risk for repeated occurrence of the condition compared to subjects without such histories.

[Slide.]

Now, in the adverse-event section, we have added a chart that calls out annual rates for selected events as seen during the FDA trial. Placing results of clinical trials in product labeling is routine for pharmaceutical agents in many medical devices. However, no other contact-lens labeling contains this type of information. We have proposed a listing of corneal inflammatory events that occurred in the trial presented in

order of most frequent to less frequent.

Additional event types and/or rates could be added to this section as proposed by the panel reviewers.

[Slide.]

In the wearing-schedule section, we have added a chart that identifies the average achieved wearing time for those who completed the one-year FDA trial. As you have heard, virtually all subjects in the Focus Night and Day group were prescribed 30 nights extended wear throughout the study duration but because of symptoms or simply lifestyle requirements, mid-month removals did occur and it was our goal to present information in the labeling that reflected the wearing experience of the subjects in the trial.

But, as mentioned earlier, there may be alternative ways of presenting information regarding wearing time that the panel recommends for this section.

[Slide.]

Also in the wearing-schedule section, we emphasized the importance of close monitoring during the first month of 30-night extended wear. We have added to the standard labeling that

patients should be monitored closely during the first month of 30-night continuous wear. If problems occur during this first month, the patient may not be suitable for the full 30-night wearing schedule.

This addition is made because many of the problems were noted in the first month of the FDA trial as described earlier. This statement is another alternative to address the reviewers' request that a statement be added that not all patients can tolerate continuous wear.

[Slide.]

In the lens-fit assessment section of the practitioner fitting guide, we had added a statement about lens-edge standoff and a separate statement about reduced comfort as often being the only signal of a loose-fitting lens. These statements are included in the section that also describes the characteristics of a well-fitting lens or tight-fitting lens and communicates that the lens should demonstrate a satisfactory push-up test and have 0.1 to 0.5 millimeters of movement with the blink.

These statements should improve early fitting performance without encouraging fitting

practices that result in excessively tight-fitting lenses.

[Slide.]

So, in summary, product labeling is an essential tool used to distribute key safety and effectiveness information to practitioners and patients. The indication of up to 30 nights extended wear is an important change from the current six-night extended-wear products and, therefore, warrants modifications for current extended-wear labeling.

As you have heard, we have taken key information from our FDA study and have used that data to modify the parts of the labeling that you see here.

[Slide.]

At this point, I would like to talk briefly about the postapproval evaluation that we have submitted.

[Slide.]

We believe that the preapproval clinical trials have given reasonable assurance that Focus Night and Day is safe and effective as indicated for up to 30 nights extended wear. The high oxygen permeability and biocompatible nature of these

lenses are the primary reason for this clinical success. However, certain important low-incidence events such as microbial keratitis require a large trial to determine the event rate.

For example, our study of over 650 subjects for a year had no cases of microbial keratitis allowing us to conclude that the rate of MK is no greater than approximately 45 in 10,000. But a postapproval evaluation will allow us to increase our confidence that the actual rate is much lower than this.

So, to address this important issue, we are working with the agency to design a postapproval evaluation. The questions we have chosen to ask during this evaluation are, number one, is the annualized microbial keratitis rate greater than 20 per 10,000 in Focus Night and Day wearers and, number two, is there vision loss in any case of microbial keratitis that is equal to two or more lines of Snellen acuity.

[Slide.]

With respect to study design and rationale, both case-control and prospective study designs were considered as alternative approaches for this postapproval evaluation. The case-control

study design was ruled out based on our current international marketing experience which predicts that it would be difficult to get sufficient numbers of microbial keratitis cases in a timely fashion.

The small number of cases of which we have been informed suggest that a case-control study may require a long case-collection phase in order to get sufficient case numbers.

During the February '98 Ophthalmic Panel Meeting, Dr. Schein recommended that these studies should be observational with simple, important outcomes recorded. He stated there should be no doubt that something significant happened.

Also at the November, 2000 Ophthalmic Panel Meeting, Dr. Bullimore commented that, in addition to simply observing the rates of important events such as MK, that the loss of best visual acuity should be noted as with refractive-surgery studies.

Finally, it was also mentioned at that November, 2000 panel meeting that a dedicated effort should be made to standardize the definition of microbial keratitis for the purpose of consistently counting endpoint events.

So these were our parameters in designing our postmarket evaluation.

[Slide.]

This is a summary of our proposed design. You can see, we have selected a single-group observational study design consisting of 2000 Focus Night and Day wearers all prescribed 30 nights extended wear.

Between 100 and 200 clinical sites will participate and the observational period will be for one year. Our endpoints will be microbial keratitis and the loss of best visual acuity of two lines or greater after resolution of MK or other inflammation.

[Slide.]

An important element of this evaluation would be the use of an independent board selected from ophthalmologists, optometrists, epidemiologists, et cetera, to define the endpoints prior to the evaluation and to review cases during the observation period.

Information will be collected from the wearer and the practitioner at three points; baseline, 6 and 12 months. Simple accountability data and a questionnaire will be completed if there

has been no event. With an infiltrative event occurring during the observational period, detailed information about the course and outcome of the information will be recorded.

The independent board will review these reports and determine if the event was a microbial-keratitis endpoint. So we feel this study design would provide important information about rare inflammatory events in a timely fashion giving us an early warning signal of an unexpectedly high incidence of microbial keratitis and would also allow us to gather more information for future improvements aimed at reducing even minor inflammation.

[Slide.]

So, at this point, I would like to make a few closing comments. We believe international premarket FDA studies and international market experience have given reasonable assurance that Focus Night and Day is safe and effective for the proposed indications.

The proposed labeling adds significant new information about product performance which should enlighten practitioners and patients about the benefits and risks of this product. We have

pointed out a few areas in the labeling that could be further enhanced. We feel we have made a pretty good start at the modifications required for this new indication.

[Slide.]

The proposed postapproval evaluation will add additional information about significant sight-threatening events in a relatively short period after market launch. This evaluation, plus information from the U.S. Medical Device Reporting System and global postmarket vigilance, will allow timely and sufficient monitoring of product performance.

This concludes the sponsor's presentation. Thank you for your attention.

DR. SUGAR: Thank you. We have about forty minutes until the proposed lunchtime. We have scheduled fifteen minutes for questions for the sponsor. Sometimes it takes longer, sometimes it takes shorter, than that. Then the FDA presentation.

I don't see many people squirming so my proposal is that we work through until lunchtime and get as far along in the program as we can, unless someone has strong objections, even weak

objections.

Then what I would like to do is ask the panel for questions of the sponsor. Alice?

DR. MATOBA: I am Alice Matoba. I have a question on the slide from Dr. McNally's presentation on study design, sample size and power. I know you expected an incidence of 8.6 percent for endpoint infiltrates in the Acuvue group and you selected an n of 500. So that gave you a power base of 7 percent.

But this table shows the power increasing as your expected incidence increases. I think that is incorrect. In fact, you found only an incidence of 3.1 percent in your Acuvue group and that would tend to decrease the power of your study. So my question is, have you reassessed the numbers to see whether, indeed, you did have adequate power to detect a 5 percent difference.

DR. McNALLY: Our goal was to determine if we had a difference from 5 percent. Indeed, we did detect a difference from 5 percent

DR. MATOBA: It was not significant.

DR. McNALLY: It was significant because we were trying to be significantly different than 5 percent in a noninferiority design. With a p of

0.046, which is -- we set the alpha at 0.05, so 0.046 being less than 0.05 says that we are statistically different than 5 percent.

DR. MATOBA: Okay. Let me just rephrase it, then. You were looking at a phenomenon that you expected to have an incidence of 8.3 percent. So you selected an n of 500. But if, actually, the phenomenon had an incidence of only 3 percent, would you not expect to need a greater n to detect a significant difference between your product and the product you are comparing it to?

DR. McNALLY: This might have to be one that we refer to the statisticians but these calculations here were based on the assumptions to prove a 5 percent difference. The power does increase as the rates go lower for this noninferiority test.

DR. MATOBA: But my second question, can you explain --

DR. McNALLY: Can we give this maybe the statistician because they can maybe explain it a little better than a clinician.

DR. CUTTER: I am Gary Cutter. I am a consultant to Ciba Vision. You are correct about power for a test of no difference between two

groups. As the event rate goes down, you would need more sample size if you were doing a null hypothesis of equality between the two groups. This is a noninferiority hypothesis so the difference of 5 percent was fixed and, therefore, as the event rate is smaller, you actually increase power because you have a bigger fixed difference relative to a smaller standard error.

You are not trying to get a difference between two groups which now has a smaller standard error. You have a fixed difference with a smaller standard error. Your power actually goes up. This study was designed with the 8.6 event rate from prevalence data and we then were being conservative if, in fact, the rate would be lower in an incidence study where you follow the patients.

I think those calculations are correct. It does have to do with the uniqueness, maybe, of the noninferiority study. But it was what I think we were attempting to do.

DR. MATOBA: Thank you.

DR. SUGAR: Dr. Bandeen-Roche, do you want to comment?

DR. BANDEEN-ROCHE: Yes. This is Karen Bandeen-Roche. I just wanted to comment that I

agree with the explanation just given. I also want to follow up with a related question which was that, certainly, the Acuvue rate was much smaller than what was projected. You just said you used a prevalence rate, but do you have any other comments? Were you surprised by the Acuvue rate being 3 percent rather than the projected 8 percent? How do you account for that?

DR. McNALLY: I can make a clinical comment on it. When we started the study, or when we designed the study which I guess would have been '98 or so, we looked for studies in the literature to say what is the expected rate with extended wear. There weren't that many studies. We could only really find one published study by Levy which said a 12 percent rate. Then we were looking for staining over the top which we explained in the report, which gave us the 8.6.

We found no other studies other than our own studies which we didn't have extensive year-long studies so there was very little data at that time. I think there has been a lot more data generated in the literature since then.

But two panels or three panels ago when we discussed extended wear, one thing that did show

out in the study is we thought that the cumulative rate of serious and significant and nonsignificant types of adverse events was about the 10 percent level. I don't know if you recall this. We came out with these 8.something and 9.something rates.

So the overall rates, I think, were pretty much in line with what was more in the literature at the time, I think, which was about a 10 percent rate of adverse events. The infiltrate rate, especially as we defined it, we really didn't have a lot go on. We took our best estimate and tried to design a study that would give us that flexibility from 12 percent to 2 percent to still have enough power to perform the noninferiority test.

DR. SUGAR: Dr. Pulido?

DR. PULIDO: Jose Pulido. I guess you chose the 5 percent because you didn't want to have a 50 percent increase over what was already out there. If the one was 10 percent, you didn't want greater than 15 percent; right?

DR. McNALLY: That's right. If we took 8.6 and you said a 5 percent, that is not even a two times increase.

DR. PULIDO: Correct.